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ORIGINAL ARTICLE

Total pancreatectomy with islet cell autotransplantation as the initial treatment for minimal-change chronic pancreatitis

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Abstract

Objectives: Patients with minimal-change chronic pancreatitis (MCCP) are traditionally managed medically with poor results. This study was conducted to review outcomes following total pancreatectomy with islet cell autotransplantation (TP/IAT) as the initial surgical procedure in the treatment of MCCP.

Methods: All patients submitted to TP/IAT for MCCP were identified for inclusion in a single-centre observational study. A retrospective chart review was performed to identify pertinent preoperative, perioperative and postoperative data.

Results: A total of 84 patients with a mean age of 36.5 years (range: 15–60 years) underwent TP/IAT as the initial treatment for MCCP. The most common aetiology of chronic pancreatitis in this cohort was idiopathic (69.0%, $n = 58$), followed by aetiologies associated with genetic mutations (16.7%, $n = 14$), pancreatic divisum (9.5%, $n = 8$), and alcohol (4.8%, $n = 4$). The most common genetic mutations pertained to *CFTR* ($n = 9$), *SPINK1* ($n = 3$) and *PRSS1* ($n = 2$). Mean ± standard error of the mean preoperative narcotic requirements were 129.3 ± 18.7 morphine-equivalent milligrams (MEQ)/day. Overall, 58.3% ($n = 49$) of patients achieved narcotic independence and the remaining patients required 59.4 ± 10.6 MEQ/day ($P < 0.05$). Postoperative insulin independence was achieved by 36.9% ($n = 31$) of patients. The Short-Form 36-Item Health Survey administered postoperatively demonstrated improvement in all tested quality of life subscales.

Conclusions: The present report represents one of the largest series demonstrating the benefits of TP/IAT in the subset of patients with MCCP.

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Introduction

Minimal-change chronic pancreatitis (MCCP) is characterized by chronic inflammatory destruction of the gland with subsequent exocrine/endocrine dysfunction and persistent abdominal pain without main duct dilation.[1] In a subset of these patients, findings are so subtle that classical imaging modalities often do not detect the findings of chronic pancreatitis (CP). These patients usually present with debilitating abdominal pain or recurrent acute pancreatitis. When present, the disease usually involves the entire gland. Traditional management strategies have historically focused on medical therapy for the control of symptoms. Exocrine dysfunction has been abated through the administration of replacement enzymes. Endocrine dysfunction and the resulting diabetes have been managed with oral hypoglycaemic medications and/or exogenous insulin administration. Attempts at pain management are made by escalating analgesic and narcotic regimens.[2]

It was commonly accepted that CP would progress to the point of organ failure or burnout, at which point the patient's abdominal pain would subside.[3] Therefore, medical management was

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considered the standard of care and narcotic medications represented an ideal bridging therapy until organ burnout occurred. Additional studies have since questioned this burnout phenomenon and demonstrated that abdominal pain persisted in the majority of patients with CP over a 10-year follow-up period.[4] In MCCP, not only does pain persist, but almost 80% of patients experience worsening functional status despite optimal medical management.[5] Given the inadequacies of medical management in MCCP, surgical intervention has been advocated for patients with refractory disease. Lateral pancreaticojejunostomy with or without limited gland resection has been widely accepted for the treatment of large duct CP,[6–9] but it does not address the underlying pathophysiology in MCCP.[10] The development of surgical interventions for the treatment of MCCP has focused on varying degrees of gland resection. Classical and pylorus-preserving pancreaticoduodenectomy (PD) have been shown to provide benefit in head-dominant disease, but the remnant gland provides a source of persistent disease.[1,11] Izbicki *et al.* and Yekebas *et al.* reported on the benefits of longitudinal excision of the ventral pancreas for small duct disease and demonstrated pain reduction in the majority of patients.[12,13] Near-total or total pancreatectomy (TP) was largely reserved for the worst cases because of its associated morbidity, but its use in the treatment of CP has been rejuvenated with advances in islet cell autotransplantation (IAT).[14–16]

At the study institution, practitioners have advocated for TP/IAT as the initial procedure for patients with MCCP. This paper reports on outcomes in a series of patients submitted to TP/IAT as the initial surgical intervention for the treatment of MCCP with an emphasis on islet yields, postoperative insulin and narcotic requirements, and standardized quality of life (QoL) assessments.

Materials and methods

Patient selection

Patients referred to the University of Cincinnati Pancreatic Disease Center were submitted to a thorough multidisciplinary team evaluation conducted by practitioners in gastroenterology, endocrinology, radiology and pancreatic surgery. Minimal-change CP was diagnosed according to the results of imaging and functional testing, and patient symptomatology that was consistent with CP but in the absence of pancreatic duct dilation. Imaging modalities included computed tomography (CT), endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP). Functional testing included the measurement of fecal fat and elastase levels in conjunction with pancreatic bicarbonate levels. In most patients, diagnosis was based on clinical symptoms and confirmed with EUS, ERCP and CT findings. Confirmation with EUS required the presence of four or more of the nine conventional criteria: parenchymal findings included hyperechoic foci, hyperechoic stranding, hyperechoic lobularity and cysts, and ductal findings included irregular duct contour, hyperechoic ductal margin, visible side branches, and ductal calculi.[17] If a patient had fewer than four (Rosemont or conventional) findings but a concomitant major finding (stones or honeycomb lobularity), that patient was diagnosed with MCCP. The confirmation of a diagnosis by ERCP was based on the Cambridge classification.[18] Patients with Cambridge II and III disease were designated as having MCCP. Patients with debilitating pain and/or a disturbed QoL despite maximal medical and endoscopic management were considered as surgical candidates. At the study institution, TP/IAT was offered to patients with MCCP as the initial surgical intervention, but was only considered in patients with type 2 diabetes mellitus if they were insulin-independent or required <0.5 units of insulin per kilogram body weight per day.

Operative procedure and islet cell transplantation

Total pancreatectomy was performed in all patients and included splenectomy and resection of the duodenum and distal common bile duct. The body and tail of the pancreas were mobilized first and the pancreatic blood supply was preserved as long as possible to minimize islet cell ischaemia. The distal pancreas was divided at the level of the superior mesenteric vein and infused with enzymatic solution through the pancreatic duct. Islet cell isolation was performed by enzymatic degradation of the pancreatic tissue as previously described.[19,20] Cell viability was confirmed with acridine orange and propidium iodine staining and alamar blue staining. Islet cells were suspended in 5% albumin solution containing heparin at 70 units per kilogram of body weight and transplanted via portal vein infusion. Roux-en-Y surgical reconstruction consisted of choledochojejunostomy and gastrojejunostomy.

Postoperative care

All patients were monitored in the surgical intensive care unit following TP/IAT for insulin infusion and strict blood glucose control (serum levels of <120 mg/dl). Patients were converted to a basal bolus insulin regimen starting on postoperative day 3. Strict glycaemic control was maintained throughout the hospitalization and all patients were discharged to home with an insulin regimen. All patients were counselled on the management of diabetes prior to hospital discharge. Insulin regimens were adjusted and weaned based on a review of patient blood glucose journals and haemoglobin A1c levels by the patient's endocrinologist.

Data collection and statistical analysis

This study was approved by the University of Cincinnati Institutional Review Board and informed consent was obtained from all study participants. The University of Cincinnati Pancreatic Disease Center patient database was reviewed to identify all patients submitted to TP/IAT for MCCP between 2002 and 2012. A retrospective chart review identified pertinent preoperative, intraoperative and postoperative details. The overall mean ± standard error of the mean (SEM) follow-up time for the patient cohort was 32.0 ± 3.4 months after TP/IAT. All medication

requirements were determined from prescriptions listed in the patients' medical records; subjective reports of narcotic use were not included. Narcotic requirements are reported as morphine-equivalent milligrams per day (MEQ/day) and were calculated using narcotic conversion software [Narcotic Converter; GlobalRPH, Inc. (http://www.globalrph.com/narcotic_converter.htm)]. Only scheduled narcotic medications were reported. Quality of life after TP/IAT was assessed in a cross-sectional manner with the Short-Form 36-Item Health Survey (SF-36) and standardized scoring module.[21,22]

Results

Patients

Eighty-four patients underwent TP/IAT as the initial surgical intervention for the treatment of MCCP at the University of Cincinnati between January 2002 and June 2012. Patient demographics are presented in Table 1. The mean patient age was 36.5 years (range: 15–60 years) and the majority were female (n = 56, 66.7%). Idiopathic MCCP was the most common aetiology (n = 58, 69.0%), followed by an identifiable predisposing genetic mutation (n = 14, 16.7%), pancreatic divisum (n = 8, 9.5%), and alcohol-induced CP (n = 4, 4.8%). In patients with identifiable genetic mutations, *CFTR* gene mutations predominated (n = 9, 64.3%), followed by *SPINK1* (n = 3, 21.4%) and *PRSS1* (n = 2, 14.3%) mutations. Specific mutations are listed in Table 1. Nine (10.7%) of the patients submitted to TP/IAT for MCCP had been diagnosed with diabetes prior to the operation. Three of these patients were insulin-dependent (mean ± SEM insulin requirement: 9.4 ± 5.6 U/day) and the remaining six were taking oral hypoglycaemic medications only.

Table 1 Demographic data for 84 patients with minimal-change chronic pancreatitis treated with total pancreatectomy with islet cell autotransplantation

Patient characteristic	Value
Age, years, mean ± SEM (range)	36.5 ± 11.8 (15–60)
Weight, kg, mean ± SEM (range)	72.1 ± 18.0 (42–116)
BMI, kg/m^2, mean ± SEM (range)	24.7 ± 6.7 (14–49)
Sex, *n* (%)	
Male	28 (33.3%)
Female	56 (66.7%)
Diabetic, *n* (%)	9 (10.7%)
Aetiology, *n* (%)	
Idiopathic	58 (69.0%)
Genetic	14 (16.7%)
CFTR	9
ΔF508	3
ΔF508 + M470V	1
ΔF508 + R117H	1
R117H	1
P750L	1
R31C	1
5T variant	1
SPINK1	3
N34S	3
PRSS1	2
R122H	1
N29I	1
Divisum	8 (9.5%)
Alcohol	4 (4.8%)

BMI, body mass index; *CFTR*, cystic fibrosis transmembrane conductance regulator; *PRSS1*, cationic trypsinogen; SEM, standard error of the mean; *SPINK1*, serine protease inhibitor, Kazal type 1.

Perioperative details

Islet cell autotransplantation was successfully performed in all patients. The mean ± SEM islet yield for the entire cohort was 440 759 ± 29 024 islet equivalents (IEQ), which represented a mean ± SEM of 6342 ± 439 IEQ per kg body weight. The mean ± SEM operative time was 556.0 ± 10.9 min, which included tissue harvesting, islet cell isolation and autotransplantation. Mean ± SEM blood loss was 577 ± 64 ml and 24 (28.6%) patients required blood transfusion. There were no perioperative deaths. The mean ± SEM length of hospital stay was 15.0 ± 0.9 days (Table 2).

Postoperative haemorrhage requiring reoperation occurred in five (6.0%) patients. Portal venous thrombosis occurred in two patients; one patient required anticoagulation and the other patient required mechanical and chemical thrombolysis. The overall 30-day readmission rate was 29.8% (n = 25). The most common reasons for readmission were infectious aetiologies and abdominal pain; however, two patients were readmitted for glycaemic control issues.

Insulin requirements

After TP/IAT, all patients were discharged from the hospital with an insulin regimen in place. The mean ± SEM insulin requirement was 17.1 ± 1.7 U/day (Table 3). At the most recent follow-up appointment [median follow-up: 17 months, interquartile range (IQR): 9.5–27.4 months], the majority of patients (52.4%, n = 44) were found to have achieved stable glycaemic control requiring little to no insulin (0–10 U/day). A total of 36.9% (n = 31) of patients were insulin-independent at the most recent follow-up. Two patients were readmitted within 30 days following TP/IAT for glycaemic control issues which required additional diabetes education and insulin regimen adjustment. Two patients experienced a period of labile glycaemic control after TP/IAT that required frequent glucose measurements, multiple insulin injections throughout the day, and frequent regimen adjustments, but were successfully transitioned to regimens that achieved stable glycaemic control. The remaining patients achieved stable glycaemic control with a mean ± SEM insulin requirement of 14.5 ± 1.8 U/day.

Table 2 Perioperative findings in 84 patients with minimal-change chronic pancreatitis treated with total pancreatectomy with islet cell autotransplantation

Operative characteristic	Value
Operative time, min, mean ± SEM (range)	556.0 ± 10.9 (325–916)
Estimated blood loss, ml, mean ± SEM (range)	577.1 ± 64.2 (75–3100)
Pancreas weight, g, mean ± SEM (range)	69.5 ± 4.3 (21.3–188.4)
Total IEQ, mean ± SEM (range)	440 759 ± 29 024 (8450–1 057 550)
IEQ per kg body weight, mean ± SEM (range)	6342 ± 439 (138–18 700)
Length of stay, days, mean ± SEM (range)	15 ± 0.9 (4–50)
Major complications, *n* (%)	
Postoperative haemorrhage	5 (6.0%)
Portal vein thrombosis	2 (2.4%)
ARDS	1 (1.2%)
Intra-abdominal abscess	8 (9.5%)
30-day readmission, *n* (%)	25 (29.8%)
Infectious	10
Abdominal pain	7
Dehydration	5
Glycaemic control	2
Pulmonary embolus	1

ARDS, acute respiratory distress syndrome; IEQ, islet cell equivalent; SEM, standard error of the mean.

Table 3 Insulin and narcotic requirements in 84 patients with minimal-change chronic pancreatitis treated with total pancreatectomy with islet cell autotransplantation

Requirement	Value
Insulin requirements, U/day, mean ± SEM	
Preoperative	1.0 ± 0.7
At discharge from hospital	17.1 ± 1.7
At 6 months	13.6 ± 2.3
Most recent follow-up[a]	14.5 ± 1.8
Independent, *n* (%)	31 (36.9%)
0–10 U/day, *n* (%)	13 (15.5%)
10–20 U/day, *n* (%)	11 (13.1%)
>20 U/day, *n* (%)	27 (32.1%)
Narcotic requirements, MEQ/day, mean ± SEM	
Preoperative	161.5 ± 20.9
At discharge from hospital	130.6 ± 12.0
At 6 months	52.9 ± 11.2
Most recent follow-up[a]	59.4 ± 10.6
Independent, *n* (%)	49 (58.3%)
<50 MEQ/day, *n* (%)	10 (11.9%)
50–200 MEQ/day, *n* (%)	17 (20.2%)
>200 MEQ/day, *n* (%)	6 (7.1%)

[a]Median most recent follow-up was 17.1 months (interquartile range: 9.5–27.4 months).
MEQ/day, morphine-equivalent milligrams of narcotics per day; SEM, standard error of the mean; U/day, units of scheduled insulin per day.

Of the nine patients in the cohort who underwent TP/IAT subsequent to a previous diagnosis of diabetes mellitus, only one was insulin-independent at the most recent follow-up. Seven of these patients achieved stable glycaemic control with a mean ± SEM daily insulin requirement of 26.9 ± 5.7 U. The remaining patient required 30 U/day of insulin and died 1 year after TP/IAT secondary to acute ethanol intoxication and diabetic ketoacidosis.

Narcotic requirements

Mean preoperative narcotic requirements were 156.8 MEQ/day (Table 3). Narcotic requirements decreased to 52.9 MEQ/day ($P = 0.006$) by 6 months after TP/IAT. Narcotic requirements at the most recent follow-up (median: 17 months; IQR: 9.5–27.4 months) were 64.3 MEQ/day and 58.3% ($n = 49$) of patients were narcotic-independent. Only 7.1% ($n = 6$) of patients continued to require high-dose (>200 MEQ/day) narcotic medications after TP/IAT.

Quality of life assessment

Patient QoL was assessed using the SF-36. Cross-sectional analysis was performed at a median of 76 months (IQR: 20–83 months) postoperatively. Mean scores for each subscale of the survey are presented in Table 4. Scores on the survey are given on a scale of 0–100, where 100 represents the best functional level. All mean subscale scores were increased from previously published baseline scores for patients with CP.[15] Thirty (88.2%) of the patients surveyed reported an overall improvement in their health in comparison with their status 1 year earlier, one patient reported no change and three reported worse overall health. Improvements in the QoL subscales after TP/IAT persisted well beyond the immediate postoperative period (Table 4). Quality of life surveys administered to patients over 5 years after TP/IAT again demonstrated improvements on all subscales from previously published baseline values and showed increases similar to those seen in patients immediately following TP/IAT (0–5 years).

Discussion

The diagnosis and management of CP have continued to evolve in line with enhanced understanding of the pathophysiology of the disease and advances in procedural capabilities. The biggest controversy relating to MCCP involves establishing the diagnosis of MCCP and clarifying whether this represents an early step in the progression of CP or its own unique disease subset.[1,2,23] Currently, there is no consensus on the definition and diagnosis of MCCP. All patients referred to the University of Cincinnati Pancreatic Disease Center undergo a thorough multidisciplinary evaluation carried out by a team that includes specialists in gastroenterology,

Table 4 Quality of life scores in patients with minimal-change chronic pancreatitis treated with total pancreatectomy with islet cell autotransplantation

SF-36 category	Overall (*n* = 34)	0–5 years (*n* = 16)	>5 years (*n* = 18)	*P*-value[a]
Physical health subscores				
Physical functioning	76.2 ± 3.7	71.3 ± 5.6	80.6 ± 4.6	0.22
Role, physical limitations	37.5 ± 7.1	31.3 ± 10.2	43.1 ± 9.8	0.43
Bodily pain	51.5 ± 4.4	48.9 ± 6.8	53.8 ± 5.7	0.59
General health	44.6 ± 3.7	47.3 ± 5.2	42.2 ± 5.2	0.51
Vitality	52.1 ± 3.2	51.3 ± 5.2	52.8 ± 3.9	0.82
Mental health subscores				
Social functioning	71.7 ± 4.5	70.3 ± 6.8	72.9 ± 5.8	0.78
Role, emotional limitations	62.7 ± 7.0	54.2 ± 10.6	70.4 ± 9.0	0.26
Mental health	74.4 ± 3.3	73.8 ± 4.7	74.9 ± 4.6	0.87
Improved health from 1 year previously, %	88.2%	87.5%	88.9%	

[a]Comparison of scores for 0–5 years and >5 years.
SF-36, Short-Form 36-Item Health Survey.

endocrinology, radiology, pain management and pancreatic surgery. At this institution, the diagnosis of MCCP is based on clinical presentation and confirmed with image findings consistent with CP in the absence of pancreatic duct dilation. The patients diagnosed with MCCP in the present cohort were not representative of the traditional CP cohort, which is largely male and in which alcohol-induced pancreatitis predominates.[2,3] In stark contrast, the present report refers to a cohort that was predominantly female and had either genetic mutation-associated or idiopathic MCCP. These observations support the diagnosis of MCCP as a separate, unique disease subset.

Establishing the diagnosis of MCCP clearly remains one of the important fundamentals in managing this difficult patient population. Endoscopic ultrasound has emerged as the predominant imaging modality in this patient group. At the study institution, the diagnosis of MCCP is confirmed by the presence of four or more of the nine conventional criteria or, in patients with fewer than four findings, at least one major finding. Using a cut-off of four criteria has been shown to provide for high sensitivity, specificity and accuracy in the diagnosis of non-calcific CP.[24] Determining the ideal cut-off for the number of criteria needed to confirm the diagnosis of CP remains controversial. Recent reports have advocated for higher criteria thresholds in establishing the diagnosis of CP.[25] Based on the present authors' clinical experience, increasing this threshold would lower the specificity of the test and result in the inappropriate treatment of patients who otherwise might benefit from surgical intervention.

Regardless of the classification, these patients present with debilitating pain that is refractory to traditional medical and endoscopic management.[1,5,23] Several institutions, including the University of Cincinnati, have developed treatment algorithms specifically tailored towards the management of patients with MCCP. The decision model in this centre's present treatment algorithm focuses on disease morphology in order to determine the ideal surgical intervention. The benefits of pancreaticoduodenectomy and duodenum-preserving pancreatic head resection have been well documented in the treatment of MCCP with isolated head disease.[1,2,26] Izbicki *et al*. and Yekebas *et al*. reported on the benefits of a novel procedure in patients with small duct disease using a longitudinal V-shaped excision of the ventral pancreas.[12,13] Despite the initial pain relief afforded by these procedures, there remains a risk for recurrent pancreatitis in the remnant gland.[11] Total pancreatectomy has traditionally been reserved for patients for whom no other options remain. However, with advances in IAT, TP has been increasingly performed for CP.[15,16,20,27] The present authors believe that the best way of achieving longterm pain relief and improved QoL in MCCP involves complete gland excision. Additionally, early intervention ensures the adequate preservation of β cell mass before progressive glandular destruction ensues and precludes a patient from IAT. Based on these established results, the present group has focused its surgical decision making on gland anatomy and disease morphology. Patients with findings of a dilated pancreatic duct or isolated focal disease are selected to undergo traditional ductal drainage procedures and/or limited pancreatic gland resection. However, in patients with findings of MCCP which are not amenable to traditional procedures, the present authors have advocated for TP/IAT as the initial surgical treatment for MCCP that is refractory to medical therapy. The current study represents the first to specifically examine outcomes of TP/IAT as the initial surgical procedure for MCCP. The current series demonstrates the hallmarks of success after TP/IAT, which include longterm pain relief, stable glycaemic control and overall improved QoL.

Chronic pain and narcotic dependence lead to lower levels of function and decreased QoL in these patients. In the present cohort, pain relief was achieved after TP/IAT with clear reductions

in narcotic requirements. A total of 58.3% ($n = 49$) of patients in the present series were narcotic-independent after the operation, which is consistent with rates in previously published reports,[15] and the remainder of patients showed significant reductions in narcotic requirements. The SF-36 questionnaire was used to assess the effects of CP, especially of chronic pain, on a patient's lifestyle. A cross-sectional analysis was performed after TP/IAT, in which 40.5% of patients were included. Outcomes on all of the subscales tested were found to have improved in comparison with previously established baseline scores[15] and 88.2% of respondents reported an overall improvement in their health. The lack of preoperative assessment is a clear limitation of this study, but the use of validated questionnaires allows for the demonstration of consistency between the improvements seen in the present cohort and those in previously published reports.[15] Additionally, these improvements persisted well beyond the immediate postoperative period, a finding that demonstrates evidence of the durability of the results seen after TP/IAT.

Stable glycaemic control achieved with minimal insulin requirements is the ultimate goal of IAT. This has a significant impact on QoL after TP/IAT, as well as a profound impact on the patient's overall health.[15] In addition to the retention of insulin-producing β cells, islet cell transplantation also provides a source of counter-regulatory hormones, including glucagon, to reduce the incidence of 'brittle' diabetes and hypoglycaemic unresponsiveness. Although insulin independence is not the primary goal of this operation, 36.9% of patients in the present series were insulin-independent after TP/IAT. Additionally, 28.6% of patients achieved stable glycaemic control with minimal (<20 U/day) insulin requirements. High islet yields are likely to have contributed to the high incidence of insulin independence and low insulin requirements.[28] The present mean islet yield of 6342 IEQ/kg body weight was higher than those in previously published series,[15,16,29] but not unexpected in this cohort, which was naïve to previous pancreatic surgery. Early education on diabetes and longterm multidisciplinary follow-up are also critical to the maintenance of successful glycaemic control after TP/IAT.

In summary, this study reports the outcomes of TP/IAT as the initial surgical procedure in a large cohort of patients with MCCP. In this patient population, establishing the correct diagnosis and classification is imperative for surgical planning. A multidisciplinary team approach remains the standard for the successful diagnosis and management of patients with CP. The treatment of refractory MCCP with TP/IAT facilitates decreased narcotic requirements, stable glycaemic control, and improved QoL, which for many patients results in a return to their daily lives. This series is the first to document the longterm (>5 years post-TP/IAT) benefits of TP/IAT as the initial surgical intervention for MCCP. Future studies are necessary to validate the subset of patients who will benefit from TP/IAT based on radiographic definitions and should further ascertain the best timing of the intervention in order to maximize the achievement of pain relief and glycaemic control.

Conflicts of interest

None declared.

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